CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-237

BIOEQUIVALENCE

Sotalol Hydrochloride
Tablets
80 mg, 120 mg, 160 mg, & 240 mg
ANDA 75-237
Reviewer: Lin-Whei Chuang

Genpharm Inc.
Etobicoke, Ontario, Canada

Submission Date:
October 14, 1998
August 17, 1999

Review of a Waiver Request and an Amendment to the Review of Two Bioequivalence Studies and Dissolution Data

Background:

Results of the bioequivalence studies conducted on the 240 mg strength and dissolution data of the 80 mg, 160 mg and 240 mg strengths were found to be acceptable by the Division of Bioequivalence on 3/25/98 with recommendation to modify the dissolution specification from "not less than 70% in 30 minutes" to "not less than 80% in 30 minutes". A waiver was granted for the 80 mg and 160 mg strengths based on 21 CFR 320.22(d)(2).

However, for consistency in the dissolution testing of this drug product with the reference drug, Betapace^{R}, a revised dissolution method was recommended by the Agency in its letter of 8/4/98. Instead of 0.1 N HCL, which had been used by the firm as dissolution medium, water was recommended to be used as the dissolution medium for this drug product.

Review:

The firm's major amendment submitted on 10/14/98 indicated that it had revised the dissolution specification to "not less than

In addition, the 120 mg was added as an amendment to the existing ANDA. The dissolution data for the 120 mg strength conducted in 0.1 N HCL is presented below in Table 1:

Table 1: Dissolution Testing of Sotalol HCL Tablets, 120 mg
Drug: Sotalol Hydrochloride Tablets Dose Strength: 120 mg ANDA No.: 75-237 Firm: Genpharm Inc. Submission Date: 10/14/98
I. Conditions for Dissolution Testing:

USP 23 Apparatus: 2 (Paddle) RPM: 50
Medium: 0.1 N HCL Volume: 900 mL
No. Units Tested: 12
Tolerance (Q): NLT of sotalol in 30 minutes
Reference Drug: Betapace® 120 mg tablets (Berlex)
Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min.)	Test Product: Sotalol HCL tablet Lot No.: AA52 Strength: 120 mg			Reference Product: Betapace® tablet Lot No.: W50119 Strength: 120 mg		
	Amount Dissolved			Amount Dissolved		
	Mean %	Range %	% CV	Mean %	Range %	% CV
5	52.63		9.73	22.88		6.11
10	85.58		4.35	43.09		9.84
15	98.15		1.72	78.12		11.19
20	99.48		0.97	96.56		2.55
30	99.44		0.78	98.88		1.03

Another amendment submitted on 8/17/99 included a waiver request for the 120 mg strength and dissolution data of all strengths (Table 2) conducted using water as the dissolution medium. Since the test batches submitted for the 80, 160 & 240 mg are all more than 2-year old, new batches manufactured with the validated process, which was described in the Master Manufacturing Document submitted in the previous amendment, were used in the following dissolution testing. For the same reason, new reference lots were also used in the following tests.

Table 2: Dissolution Testing of Sotalol HCL Tablets, 80, 120, 160, and 240 mg

Drug: Sotalol Hydrochloride Tablets
Dose Strength: 120 mg
ANDA No.: 75-237
Firm: Genpharm Inc.
Submission Date: 8/17/99

I. Conditions for Dissolution Testing:

USP 23 Apparatus: 2 (Paddle) RPM: 50
Medium: Water Volume: 900 mL
No. Units Tested: 12
Tolerance (Q): of sotalol in 30 minutes
Reference Drug: Betapace® 120 mg tablets (Berlex)
Assay Method: rption 227 nm

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min.)	Test Product: Sotalol HCL tablet Lot No.: AE081 Strength: 80 mg	Reference Product: Betapace® tablet Lot No.: W60188(Exp. 12/99) Strength: 80 mg

	Amount Dissolved			Amount Dissolved		
	Mean %	Range %	% CV	Mean %	Range %	% CV
5	36.7		20.58	31.0		8.77
15	88.9		6.22	91.0		3.20
30	101.1		2.42	101.1		1.22
60	101.8		0.43	101.2		1.32
Sampling Times (min.)	Test Product: Sotalol HCL tablet Lot No.: AA521 Strength: 120 mg			Reference Product: Betapace® tablet Lot No.: 1W90048 (Exp. 03/03) Strength: 120 mg		
	Amount Dissolved			Amount Dissolved		
	Mean %	Range %	% CV	Mean %	Range %	% CV
5	39.7		14.83	38.2		13.19
15	94.2		2.12	92.1		2.12
30	99.9		0.8	98.6		1.20
60	100.2		1.05	98.7		1.41
Sampling Times (min.)	Test Product: Sotalol HCL tablet Lot No.: AE111 Strength: 160 mg			Reference Product: Betapace® tablet Lot No.: W80170 (Exp. 10/99) Strength: 160 mg		
	Amount Dissolved			Amount Dissolved		
	Mean %	Range %	% CV	Mean %	Range %	% CV
5	28.9		18.95	23.5		15.47
15	80.6		8.26	84.4		4.83
30	100.0		0.81	99.9		1.89
60	100.6		0.85	100.3		1.16
Sampling Times (min.)	Test Product: Sotalol HCL tablet Lot No.: AE181 Strength: 240 mg			Reference Product: Betapace® tablet Lot No.: W80282 (Exp. 01/2003) Strength: 240 mg		
	Amount Dissolved			Amount Dissolved		
	Mean %	Range %	% CV	Mean %	Range %	% CV
5	30.19		15.52	21.5		10.73
15	79.3		6.71	80.1		2.96
30	99.2		0.51	98.7		1.81
60	100.0		0.47	99.8		0.96

Comparative formulation of all strengths of the firm's sotalol tablets are presented below in Table 3:

Table 3: Comparative Formulations of Test Drug Product

	80 mg	120 mg	160 mg	240 mg
	mg per Tablet (% of Total Tablet Weight)			
Sotalol Hydrochloride	80.00 (40.0)	120.00 (40.0)	160.0 (40.0)	240.0 (40.0)
Starch				

Microcrystalline Cellulose	
Lactose	
Colloidal Silicone Dioxide	
Stearic Acid	
Magnesium Stearate	
Purified Water	
Total Weight	

Comments:

1. Sotalol HCL is freely soluble in water. The dissolution data of all strengths from batches manufactured with the same validated process as that used for the bio lots are acceptable. The F2 values were 66.6, 58.5 and 94.7 for the 80 mg, 120 mg and 160 mg strength, respectively, when compared to the 240 mg strength which had undergone bioequivalence studies with acceptable outcome.

2. Comparative formulations of all 4 strengths of the test drug product show them to be proportionally identical for the active and inactive ingredients.

3. Comparative formulations of all strengths of the reference listed drug, Betapace® presented below in Table 4 show proportionality only between the 160 mg and 240 mg strengths.

Table 4: Comparative Formulations of Reference listed Drug Product				
	80 mg	120 mg	160 mg	240 mg
	mg per Tablet (% of Total Tablet Weight)			
Sotalol Hydrochloride	80.00	120 (20.0)	160.0 (40.05)	240.0 (40.0)
Starch				
Cellulose				
Stearic Acid				
Dye FDC Blue				
Lactose				
Magnesium Stearate				
Silicone Dioxide				
Total Weight				

PNG = Potency Not Given, NG = Not Given

Recommendation:

1. The fasting bioequivalence study conducted by Genpharm Inc. on its sotalol hydrochloride 240 mg tablets, lot #105172 (bulk lot #104820), comparing it to Betapace^{R} 240 mg, lot #1W50044, has previously been found acceptable by the Division of Bioequivalence on 3/25/98.

2. The food bioavailability study conducted by Genpharm Inc. on its sotalol hydrochloride 240 mg tablets, lot #105172 (bulk lot #104820), comparing it to Betapace^{R} 240 mg, lot #1W50044, has previously been found acceptable by the Division of Bioequivalence on 3/25/98.

3. The dissolution tests conducted by Genpharm Inc. on its sotalol hydrochloride tablets, 80 mg, 120 mg, 160 mg, 240 mg, have been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

   Not less than of the labeled amount of sotalol in the dosage form is dissolved in 30 minutes.

4. The waiver of bioequivalence requirements for the 80 mg, 120 mg and 160 mg strengths of the test product is granted per 21 CFR 320.22(d)(2).

Lin-Whei Chuang 8/24/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

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FT INITIALLED YHUANG 8/24/99

Concur Date: 8/30/99
for Dale Conner, Pharm. D.
Director, Division of Bioequivalence

Sotalol Hydrochloride
Tablets
80 mg, 160 mg, & 240 mg
ANDA 75-237
Reviewer: Lin-Whei Chuang

Genpharm Inc.
Etobicoke, Ontario, Canada

Addendum to Review of Two Bioequivalence Studies and Dissolution Data

Results of the bioequivalence studies and dissolution data were found to be acceptable by the Division of bioequivalence previously on 3/25/98.

However it was noted that the dissolution method employed by Bristol-Myers company for the approval of RLD (NDA #19-865 approved on 10/20/92, yet it is Berlex that presently markets the RLD, Betapace^{R}) used water as the dissolution medium.

For consistency in the dissolution testing of this drug product, the firm is advised to repeat the dissolution testing using the following method and submit the dissolution data to the Agency for review:

Apparatus: USP 2 (Paddle), 50 rpm
Medium: Water, 900 mL
Sampling Times: 5, 15, 30 and 60 minutes
Tolerance: Not less thar n 30 minutes

Lin-Whei Chuang 7/21/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 7/22/99

Concur Dale P. Conner Date: 7/23/99
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

Sotalol Hydrochloride Tablets
80 mg, 160 mg, & 240 mg
ANDA 75-237
Reviewer: Lin-Whei Chuang

Genpharm Inc.
Etobicoke, Ontario, Canada

Submission Date:
October 30, 1997
November 20, 1997
November 24, 1997

Review of Two Bioequivalence Studies, Dissolution Data and Waiver Request

Introduction:

Sotalol hydrochloride is a non-selective β-adrenergic blocking agent. Like propranolol, sotalol inhibits response to adrenergic stimuli by competitively blocking β_1-adrenergic receptors within the myocardium and β_2-adrenergic receptors within bronchial and vascular smooth muscle. Sotalol, like propranolol, exhibits antiarrhythmic activity. Sotalol does not exhibit intrinsic sympathomimetic activity. Commercially available sotalol is a racemic mixture of 2 optical isomers. Both isomers possess antiarrhythmic activity, but only the l-isomer exhibits β-blocking activity.

Sotalol is well absorbed (90-100%) after oral administration. Maximum plasma concentrations are observed 2-4 hours after dosing. The binding of sotalol to plasma proteins is limited. It is eliminated primarily via renal excretion. The terminal elimination half-life is 12 hours (ranges between 10-15 hours). Its absorption was reduced by 20% compared to fasting when administered with a standard meal.

For the suppression and prevention of life-threatening ventricular tachyarrhythmias in adults, the usual initial dosage of sotalol hydrochloride is 80 mg twice daily. If necessary, dosage may be increased gradually after appropriate evaluation to 240-320 mg daily given in divided doses, allowing 2-3 days between dosing increments. The usual adult maintenance dosage is 160-320 mg given in 2 or 3 divided doses daily.

The reference listed drug is Betapace^R 240 mg tablets marketed by Berlex Laboratories, Inc. approved by the Agency on 10/30/92 (NDA #19865). It is also available in 80 mg and 160 mg strengths.

The firm's submission of 10/30/97 did not contain the long-term stability data and had different test product lot number for bioequivalence studies and dissolution testing. They were amended and clarified in the subsequent submissions of 11/20/97 and 11/24/97.

Bioequivalence Study under Fasting Condition - 1 x 240 mg (Study #1696-1)

The protocol of the study was dated 03/12/97. The objective of this study was to compare the rate and extent of absorption of Genpharm's sotalol 240 mg tablet and Berlex's Betapace^{R} 240 mg tablet following administration of a 240 mg dose under fasting condition.

The study was conducted at Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada . The study director was Dr. Bhaswat Chakraborty, and the medical director and principal investigator was Dr. Paul Tam. The clinical procedure was conducted during 5/5-9 & 12-16/97 and the analytical procedure was conducted during 6/5-7/4/97. The maximal possible storage period for the plasma samples of the this study was 59 days.

The design was a single-dose, 2-way crossover study. The protocol and the informed consent form were approved by the Institutional Review Board of Biovail Corporation International on 04/09/97.

Twenty-six male (26) volunteers (21 Caucasians and 5 Blacks), 19-43 years old, with the following inclusion and exclusion criteria were enrolled:

Inclusion Criteria

1. Non-smoking male between 18 and 45 years of age, inclusive.
2. Body weight not more than ±10% of the ideal weight for the subject's height.
3. Availability of subject for the entire study period and willingness to adhere to protocol requirements, as evidenced by a signed, written Informed Consent Form.
4. Normal findings in the physical examination, vital signs and ECG.
5. Negative for drugs of abuse, Hepatitis C, Hepatitis B surface

antigen and HIV.

6. No clinical laboratory values of more than ±10% outside the laboratory's stated normal range, unless the Investigator decides they are not clinically significant and records this on the case report form.

Exclusion Criteria

1. Known history of hypersensitivity to sotalol HCl and/or related drugs.
2. Known history or presence of cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
3. Known history of asthma, chronic bronchitis or other bronchospastic condition.
4. Any clinically significant illness during the last four weeks prior to entry into this study.
5. Presence of any significant physical or organ abnormality.
6. Any subject requiring maintenance therapy with any drug, or a history of drug dependency, or serious psychological disease.
7. Regular use of medication, abuse of alcoholic beverages, or participation in a clinical trial with an investigational drug, including MAO inhibitors, within 30 days preceding this study.
8. Use of enzyme-inducing and enzyme-inhibiting drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to entry into this study.
9. Use of any drugs similar to the one under study, or administration of any medication (including over-the-counter preparations) within 14 days preceding entry into this study.
10. Blood donation not exceeding 250 mL within the previous 30 days.

Volunteers were instructed not to take any medication for 14 days preceding the study and throughout the blood collection period; and not to consume any alcohol- or xanthine-containing beverages and foods for 48 hours before dosing.

After an overnight fast, in the morning of 05/06/97, each subject was given one of the following treatments according to the randomly assigned sequence:

Treatment A (Test Drug): Sotalol HCl tablet, 1 x 240 mg, Genpharm Inc., lot #105172 (from the bulk lot #104820), potency 98.9% and batch size tablets.

Treatment B (Reference Drug): Betapace^{R} tablet, 1 x 240 mg, Berlex Laboratories, lot #1W50044, potency 98.2%, expires 6/98.

Each treatment was taken with 240 mL of water. After a 7-day washout period, on 5/13/97, each subject was crossed over to the alternate treatment. Blood samples were obtained at pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5,6 ,8, 10, 12, 16, 24, 36, 48, and 72 hours after dosing. Subjects remained at the clinical site from the evening prior to dosing and until the 24-hour blood draw. They would return for the 36, 48, and 72 hour post-dose blood draws.

Subjects did not engage in any strenuous activity during the study and remained ambulatory for 1 hour post-dose. Standardized meals were served at 4.5 and 9.5 hours post-dose. Water was provided *ad libitum* except the period of 1 hour pre-dose to 1 hour post-dose, when the only fluid allowed was the 240 mL of water given with each treatment.

Vital signs were monitored before dosing and at 2 and 4 hours post-dose.

Plasma samples were stored at -70°C at the clinical site and at -22°C at the analytical site until assayed.

<u>Analytical Method -- **Not for Release through FOI:**</u>

Pre-Study Validation:

The concentrations of sotalol in human plasma were determined using ion. Plasma samples with added internal standard were extracted with

The pre-study validation performed during 4/25-5/3/97 included duplicates of 5 standard curves (9-point with range of 10-2563.4 ng/mL), each with 6 sets of 5 levels of QC samples (15.0, 30.1, 60.1, 480.6, and 1922.6 ng/mL).

A weighted ($1/conc.^2$) linear regression analysis was used. The correlation coefficients were ≥ 0.9985.

The precision was 1.67-4.97% CV for standards and 1.59-3.36% CV for QC samples. The accuracy was 95.69-102.46% for standards and 95.65-102.78% for QC samples.

The limit of reliable quantitation was set at the concentration of the lowest non-zero standard, 10.0 ng/mL. The precision and accuracy at this concentration (4.97% CV and 98.75% respectively) are acceptable.

The specificity of the method was demonstrated by the lack of significant interferences in the chromatograms of 8 individual sources. However, there was a peak co-eluted with the internal standard with peak height less than 10% of internal standard which is consistent throughout the entire analysis..

Recovery was estimated by comparing the peak heights of extracted QC samples to those of neat samples (excluding the lowest QC). The recovery rate was 64.4-68.9% for sotalol and 70.7% for the internal standard.

The stability data of sotalol evaluated under various conditions are shown below in Table 1:

Table 1: Stability of Sotalol

Condition	Stability (%)
Two levels of QC samples stored at room temperature for 4 hours before extraction	99.1-99.6
Two levels of QC sample extracts stored in the autosampler for 72 hours	97.59-98.65
Two levels of QC samples assayed after 3 freeze/thaw cycles	98.1-101.4
Long term stability - stored at -70°C for 62 days (4/24-625/97)	90.8-94.3%

During the analysis of the study samples, 13 standard curves were conducted, each with duplicates of 4 levels of QC samples (30.1, 60.1, 480.6, and 1922.6 ng/mL). The correlation coefficients were ≥0.9979. The precision was 1.91-3.67% CV for standards and 3.46-5.43% CV for QC samples. The accuracy was 99.02-101.46% for standards and 98.54-100.77% for QC samples.

Comment on the Analytical Method:

The analytical method and validation results are acceptable.

Results:

All 26 subjects completed the study. The analytical, pharmacokinetic and statistical determination were conducted using data from the first 24 evaluable subjects as stated in the protocol.

Vital sign monitoring did not revealed any significant abnormalities. Only 2 significant protocol deviations were reported: The 24-hour blood sample of subject #17 during treatment B, period 1; and the 48-hour blood sample of subject #24 during treatment A, period 2, were not collected due to misunderstanding of the study schedule by the subject and family emergency, respectively.

Six adverse events were reported by 4 subjects, all during period 2, (2 had treatment A and 2 had treatment B). The nature of these events were dizziness, lightheadedness, chest pain, and syncope. All were not drug-related except that syncope was attributed to blood draws.

The plasma samples from 24 subjects were assayed for sotalol. Among the 826 plasma samples analyzed, none was repeated due to pharmacokinetic anomaly. Only two samples were *not reportable* because there were no samples collected (see protocol deviation).

The mean plasma concentrations of sotalol at each sampling time point after both treatments are presented in Figure 1. The same data and the mean pharmacokinetic parameters are presented below in Tables 2-3.

Table 2: ARITHMETIC MEAN OF PLASMA SOTALOL LEVELS (NG/ML) AND RATIOS OF MEANS
--1X240 MG UNDER FASTING CONDITION--- (N=24 EXCEPT WHEN INDICATED)

	MEAN-TEST	SD	MEAN-REF.	SD	RATIO T/R
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	167.80	119.41	98.64	82.62	1.70
0.67	634.28	288.78	595.01	203.08	1.07
1	960.75	446.75	919.86	334.04	1.04
1.5	1377.74	643.23	1204.63	477.15	1.14
2	1594.99	599.90	1353.84	405.75	1.18
2.5	1639.06	382.86	1559.80	411.66	1.05
3	1656.46	316.61	1624.79	384.10	1.02
3.5	1580.92	318.51	1628.58	373.31	0.97
4	1549.84	276.98	1611.21	331.08	0.96
5	1471.17	270.69	1539.80	287.48	0.96
6	1294.09	239.86	1354.51	246.92	0.96
8	1065.86	197.92	1130.68	227.92	0.94
10	897.21	161.89	945.73	179.92	0.95
12	714.14	140.80	749.39	142.92	0.95
16	523.73	109.08	549.13	112.11	0.95
24	278.32	70.08	305.91	75.45	0.91
36	123.31	46.31	132.55	46.76	0.93
48	60.44	26.96	64.67	26.54	0.93
72	9.54	14.21	9.80	14.72	0.97

TABLE 3: PHARMACOKINETIC PARAMETERS FOR TEST AND REFERENCE PRODUCTS
- ARITHMETIC MEANS AND RATIOS OF MEANS -
- 1X240 MG UNDER FASTING CONDITION, N=24 -

	TEST MEAN	SD	REF. MEAN	SD	RATIO T/R
PARAMETER					
AUCI	24097.00	4694.87	25006.84	4679.69	0.96
AUCT	23413.60	4627.30	24335.50	4650.53	0.96
CMAX	1944.43	439.99	1842.72	296.78	1.06
KE	0.06	0.01	0.07	0.01	0.99
LAUCI	*23570.93	--	*24597.03	--	**0.96
LAUCT	*22885.89	--	*23917.63	--	**0.96
LCMAX	*1897.33	--	*1819.45	--	**1.04
THALF	11.11	2.34	11.01	2.32	1.01
TMAX	2.90	1.24	3.06	1.09	0.95

* = Geometric Mean ** = Ratio of Geometric Mean

The ratios of test to reference products of 3 major pharmacokinetic parameters are presented in Table 4:

TABLE 4: RATIOS OF TEST TO REFERENCE PRODUCTS OF THREE MAJOR PHARMACOKINETIC PARAMETERS
-- 1 X 240 MG UNDER FASTING CONDITION --

SUB	SEQ	AUCT	AUCI	CMAX
1	2	0.99	0.99	1.15
2	2	1.02	1.01	1.35
3	2	0.98	0.99	1.02
4	2	0.55	0.56	0.57
5	2	0.96	0.95	1.10
6	2	0.85	0.86	1.04
7	2	0.94	0.94	0.96
8	2	1.02	1.01	1.27
9	2	0.93	0.93	1.04

10	2	0.88	0.88	0.87
11	2	0.87	0.85	1.01
12	2	1.10	1.10	1.43
13	2	0.94	0.94	1.00
14	2	1.02	1.02	1.02
15	2	0.98	0.97	0.97
16	2	1.07	1.08	0.98
17	2	0.90	0.91	1.03
18	2	1.18	1.16	1.16
19	2	0.98	0.99	0.96
20	2	0.93	0.94	0.99
21	2	0.87	0.87	0.92
22	2	1.21	1.20	1.65
23	2	1.03	1.02	1.00
24	2	0.99	1.02	0.98
MEAN		0.97	0.97	1.06
N		24	24	24
MINIMUM		0.55	0.56	0.57
MAXIMUM		1.21	1.20	1.65

The mean ratio of AUCT/AUCI was 0.97 (0.94-0.99) during treatment A and 0.97 (0.94-0.98) during treatment B.

Analysis of Variance was performed on the untransformed and log-transformed data of AUCT, AUCI and CMAX. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term with a 10% level of significance. The treatment and period effect were tested against the residual mean square error with a level of significance of 5%. No significant effects were detected for any of the parameters.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of reference product versus test product are presented in Table 5.

TABLE 5: LS MEANS (LSM) AND 90% CONFIDENCE INTERVALS (CI) -- 1 X 240 MG UNDER FASTING CONDITION -- (N = 24)

	TEST LSM	REF.LSM	RATIO T/R	90% CI
AUCI	24097.00	25006.84	0.96	92.32 - 100.41
AUCT	23413.60	24335.50	0.96	92.05 - 100.37
CMAX	1944.43	1842.72	1.06	98.16 - 112.88
LAUCI	*23570.93	*24597.03	**0.96	91.00 - 100.91
LAUCT	*22885.89	*23917.63	**0.96	90.75 - 100.89
LCMAX	*1897.33	*1819.45	**1.04	97.20 - 111.88

* = Geometric LS Mean, ** = Ratio of Geometric LS Means

Comments:

1. The computation of pharmacokinetic parameters and 90%

confidence intervals has been confirmed by the reviewer.

2. The results of this fasting bioequivalence study are acceptable.

Bioequivalence Study under Non-Fasting and Fasting Conditions - 1 x 240 mg (Study #1850)

The protocol of the study was dated 03/17/97. The objective of this study was to compare the effect of food on the rate and extent of absorption of Genpharm's sotalol 240 mg tablet following administration of a 240 mg dose under non-fasting and fasting conditions and Berlex's Betapace^{R} 240 mg tablet administration of a 240 mg dose under non-fasting condition.

The study was conducted at Biovail Corporation International, Contract Research Division, Toronto, Ontario, Canada . The study director was , and the medical director and principal investigator was Dr. Paul Tam. The clinical procedure was conducted during 5/30-6/3, 6/6-10, & 6/13-17/97; and the analytical procedure was conducted during 7/8-25/97. The maximal possible storage period for the plasma samples of the this study was 55 days.

The design was a single-dose, 3-period, 3 way crossover study. The protocol and the informed consent form were approved by the Institutional Review Board of Biovail Corporation International on 04/09/97.

Twenty-one male (21) volunteers (20 Caucasians and 1 Oriental), 21-42 years old, with the same inclusion and exclusion criteria as in the fasting study were enrolled.

Volunteers were instructed with the same restrictions as in the fasting study with regards to food and beverage intake physical activities and confinement at the clinical site.

After an overnight fast, in the morning of 5/31/97, 6/7/97, and 6/14/97, each subject was given one of the following treatments according to one of 6 sequences (ABC, BCA, CAB, ACB, BAC, & CBA) randomly assigned :

Treatment A (Test Drug): Sotalol HCl tablet, 1 x 240 mg,

Genpharm Inc., lot #105172 (from the bulk lot #104820), potency 98.9% and batch size tablets, administered 5 minutes after the completion of a standard high-fat breakfast.

Treatment B (Reference Drug): Betapace^{R} tablet, 1 x 240 mg, Berlex Laboratories, lot #1W50044, potency 98.2%, expires 6/98, administered 5 minutes after the completion of a standard high-fat breakfast.

Treatment C (Test Drug): Sotalol HCl tablet, 1 x 240 mg, Genpharm Inc., lot #105172 (from the bulk lot #104820), potency 98.9% and batch size tablets, administered under fasting condition.

Blood samples were obtained at the same time schedule as in the fasting study and the plasma storage conditions were also the same.

Procedures of vital sign monitoring was the same as that in the fasting study.

Analytical Method -- **Not for Release through FOI:**

The same validated assay method (except long-term stability validation) was conducted for the analysis of sotalol in the study samples.

During the analysis of the study samples, 19 standard curves were conducted, each with duplicates of 4 levels of QC samples (30.1, 60.1, 480.6, and 1922.6 ng/mL). The correlation coefficients were $\geq$0.9988. The precision was 1.31-3.22% CV for standards and 2.13-7.05% CV for QC samples. The accuracy was 98.56-101.74% for standards and 98.57-101.23% for QC samples.

Comment on the Analytical Method:

The precision and accuracy data obtained during the analysis of study samples are acceptable.

Results:

All 21 subjects completed the study. The analytical, pharmacokinetic and statistical determination were conducted using the data from the first 18 evaluable subjects as stated in the protocol.

Vital sign monitoring did not revealed any significant abnormalities. No significant protocol deviation was reported.

One (1) adverse event was reported by subject #3 about a mild case of drowsiness.

The plasma samples from 18 subjects were assayed for sotalol. Among the 1080 plasma samples analyzed, none was repeated due to pharmacokinetic anomaly.

The mean plasma concentrations of sotalol at each sampling time point after all 3 treatments are presented in Figure 2. The same data and the mean pharmacokinetic parameters are presented below in Tables 6-7.

Table 6: ARITHMETIC MEAN OF PLASMA SOTALOL LEVELS (NG/ML) AND RATIOS OF MEANS --1X240 MG UNDER NON-FASTING AND FASTING CONDITIONS, N = 18---

	TEST-FED	SD	REF.-FED	SD	TEST-FASTING	SD	TEST-FED/REF.-FED
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.33	14.84	35.98	14.67	31.05	183.99	170.29	1.01
0.67	174.28	233.44	153.52	160.80	637.56	326.18	1.14
1	404.55	365.60	448.32	385.70	892.86	351.29	0.90
1.5	836.05	534.99	865.92	529.33	1230.35	403.84	0.97
2	1181.21	501.43	1210.70	449.47	1494.19	469.75	0.98
2.5	1415.78	409.53	1448.45	380.09	1625.98	406.60	0.98
3	1478.39	296.53	1540.67	327.37	1638.43	330.66	0.96
3.5	1461.82	236.49	1565.49	288.26	1589.98	274.48	0.93
4	1428.47	211.66	1535.30	277.32	1499.29	256.27	0.93
5	1419.57	237.65	1411.31	262.53	1406.20	241.18	1.01
6	1259.44	195.21	1243.68	231.20	1230.62	216.17	1.01
8	1016.61	155.44	1013.96	164.66	1011.46	151.85	1.00
10	861.86	138.94	858.14	138.00	875.33	143.66	1.00
12	681.73	117.73	675.16	107.25	677.23	108.27	1.01
16	501.88	91.94	491.09	82.16	500.94	79.46	1.02
24	278.09	61.61	272.01	56.58	274.95	56.76	1.02

36	121.54	40.28	118.68	33.51	119.04	35.02	1.02
48	62.34	22.55	55.81	21.12	59.25	22.67	1.12
72	11.00	14.50	4.67	10.93	8.88	13.19	2.36

TABLE 7: PHARMACOKINETIC PARAMETERS FOR TEST AND REFERENCE PRODUCTS
- ARITHMETIC MEANS AND RATIOS OF MEANS -
- 1X240 MG UNDER NON-FASTING AND FASTING CONDITIONS, N=18 -

	TEST-FED	SD	REF.-FED	SD	TEST-FASTING	SD	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
PARAMETER								
AUCI	22412.98	3437.19	22099.54	3287.42	23207.80	3779.17	1.01	0.97
AUCT	21742.12	3437.78	21417.12	3179.58	22608.21	3789.81	1.02	0.96
CMAX	1674.41	296.87	1716.55	324.15	1826.62	356.22	0.98	0.92
KE	0.06	0.01	0.07	0.01	0.07	0.01	0.93	0.95
LAUCI	22155.27	0.16	21847.06	0.16	22920.78	0.16	1.01	0.97
LAUCT	21477.79	0.16	21172.06	0.16	22313.33	0.17	1.01	0.96
LCMAX	1648.07	0.19	1684.04	0.21	1794.48	0.19	0.98	0.92
THALF	11.61	2.83	10.47	1.81	10.87	2.20	1.11	1.07
TMAX	3.31	1.11	3.08	0.79	2.81	0.84	1.07	1.18

The ratios of test to reference products of 3 major pharmacokinetic parameters of are presented in Table 8:

TABLE 8: RATIOS OF TEST TO REFERENCE PRODUCTS OF THREE MAJOR PHARMACOKINETIC PARAMETERS
-- 1 X 240 MG UNDER NON-FASTING CONDITION --

SUB	SEQ	RAUCT	RAUCI	RCMAX
1	4	1.19838	1.19061	1.14577
2	4	0.95466	0.96377	1.12506
3	6	0.94006	0.93402	0.83323
4	1	1.14002	1.12635	1.11269
5	5	0.99709	1.01249	0.77064
6	6	1.00361	0.99878	0.90212
7	1	0.88301	0.88109	0.95849
8	5	0.99847	1.02051	0.89538
9	3	1.06461	1.02882	0.90536
10	2	0.93325	0.94747	1.04270
11	1	1.11870	1.12732	1.15817
12	3	0.94668	0.95309	0.88622
13	3	1.01251	1.01136	0.96258
14	2	1.06457	1.05060	1.04750
15	4	0.99944	0.99204	0.98389
16	6	1.02315	1.02754	1.18783
17	5	0.97330	0.97453	0.98981
18	2	1.06008	1.06044	0.84125
MEAN		1.02	1.02	0.99
N		18	18	18
MINIMUM		0.88	0.88	0.77
MAXIMUM		1.20	1.19	1.19

The mean ratio of AUCT/AUCI was 0.97 (0.95-0.99) during treatment A, 0.97 (0.95-0.98) during treatment B, and 0.97 (0.95-0.99) during treatment C.

Analysis of Variance was performed on the untransformed and log-transformed data of AUCT, AUCI and CMAX. The model included sequence, subject within sequence, treatment and period as factors. The LS means of the non-transformed and log-transformed pharmacokinetic parameters, and ratios of these means are presented in Table 9.

TABLE 9: LS MEANS (LSM) AND RATIOS OF THESE MEANS
-- 1 X 240 MG UNDER NON-FASTING AND FASTING CONDITIONS -- (N = 18)

PARAMETER	TEST-FED	REF.-FED	TEST-FASTING	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
AUCI	22412.98	22099.54	23207.80	1.01	0.97
AUCT	21742.12	21417.12	22608.21	1.02	0.96
CMAX	1674.41	1716.55	1826.62	0.98	0.92
LAUCI	*22155.27	*21847.06	*22920.78	**1.01	**0.97
LAUCT	*21477.79	*21172.06	*22313.33	**1.01	**0.96
LCMAX	* 1648.07	*1684.04	*1794.48	**0.98	**0.92

* = Geometric LS Mean, ** = Ratio of Geometric LS Means

Comments:

1. The computation of pharmacokinetic parameters and LS means has been confirmed by the reviewer.

2. The test and reference drugs were absorbed to almost the same extent and at almost the same rate under post-prandial conditions.

3. When comparing bioavailability under fed and fasting conditions, the effect of food on the absorption of sotalol was negligible. This is different from the labeling of Betapace^{R} that its absorption was reduced by 20% compared to fasting when administered with a standard meal.

4. Results of this non-fasting and fasting study are acceptable.

Dissolution:

The comparative dissolution profiles of the test and reference products as conducted by the firm are presented below in Table 10:

Table 10 - In Vitro Dissolution Testing

Drug (Generic Name): Sotalol Hydrochloride
Dosage Form: Tablet
Dose Strength: 80, 160, and 240 mg
ANDA No.: 75-237
Firm: Genpharm Inc.
Submission Date: 10/30/97

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50 No. Units Tested: 12
Medium: 0.1 N HCl Volume: 900 mL
Tolerance: NLT [illegible] 30 minutes
Reference Drug: Betapace® tablets (Berlex)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Lot # 104820 (also 105172) Strength (mg): 240			Reference Product Lot # 1W50044 Strength (mg): 240		
	Mean %	Range	%CV	Mean %	Range	%CV
5	56.8		10.9	20.7		9.9
10	91.5		2.3	75.4		16.1
15	98.3		0.5	95.4		35.1
20	99.0		0.5	98.1		1.6
30	99.0	[illegible]	0.5	98.8	[illegible]	1.2

Sampling Times (minute)	Test Product Lot # 105167 (also 104819) Strength (mg): 160			Reference Product Lot # W60170 Strength (mg): 160		
	Mean %	Range	%CV	Mean %	Range	%CV
5	67.8		6.8	24.2		6.8
10	96.7		1.6	54.1		10.2
15	99.7		0.7	87.9		8.0
20	99.7		0.8	99.4		1.2
30	99.5	[illegible] .7	0.7	100.0		0.8

Sampling Times (minute)	Test Product Lot # 105165 (also 104818) Strength (mg): 80			Reference Product Lot # W60188 Strength (mg): 80		
	Mean %	Range	%CV	Mean %	Range	%CV
5	53.1		9.4	34.4		5.6

10	87.5		4.4	82.5		8.0
15	97.6		0.8	99.0		2.0
20	98.3		1.0	100.1		1.1
30	98.0		0.9	99.8	[illegible] - 101.7	1.2

Comments:

1. Sotalol hydrochloride is not an USP product. However, these dissolution results comply with the firm's specification of "not less tha: dissolved in 30 minutes".

2. **Not Releasable through FOI** -- The dissolution method employed by Bristol-Myers company (the company that owned [illegible] ıpace^{R}), was the same except that the dissolution medium was water, the sampling times were 5, 15, 30, and 60 minutes, and the specification was "not less than dissolved in 30 minutes".

3. From the firm's results, it was shown that sotalol HCl is also soluble in 0.1 N HCl and they also support a specification of "not less than dissolved in 30 minutes". The firm's method is acceptable, however, a higher specification is suggested.

Formulation:

Dosage Strength			80 mg		160 mg		240 mg	
No.	Ingredient	Std	Amount per Tablet (mg)	Amount per Tablet (%)	Amount per Tablet (mg)	Amount per Tablet (%)	Amount per Tablet (mg)	Amount per Tablet (%)
1.	Sotalol Hydrochloride		80.00	40.0	160.0	40.0	240.0	40.0
2.	Starch (Starch							
3.	Microcrystalline Cellulose							

4.	Lactose	NF	
5.	l Silicon	NF	
6.	Stearic Acid	NF	
7.	Magnesium Stearate	NF	
8.	Purified Water	USP	--
Tablet Weight			00%

Waiver Request:

The firm requests waiver of requirements for *in vivo* bioequivalence testing on its 80 mg and 160 mg products per 21 CFR section 320.22(d)(2).

Comments:

1. Both bioequivalence studies on the 240 mg strength are acceptable.

2. The dissolution data of all 3 strengths meet the specification of "not less tha dissolved in 30 minutes".

3. The formulations of 80 mg and 160 mg strengths are proportionally identical to the 240 mg strength in their active and inactive ingredients.

4. The waiver of requirements for *in vivo* bioequivalence testing on the 80 mg and 160 mg products can be granted per 21 CFR section 320.22(d)(2).

Recommendation:

1. The fasting bioequivalence study conducted by Genpharm Inc.

on its sotalol hydrochloride 240 mg tablets, lot #105172 (bulk lot #104820), comparing it to Betapace^{R} 240 mg, lot #1W50044, has been found acceptable by the Division of Bioequivalence.

2. The non-fasting and fasting bioequivalence study conducted by Genpharm Inc. on its sotalol hydrochloride 240 mg tablets, lot #105172 (bulk lot #104820), comparing it to Betapace^{R} 240 mg, lot #1W50044, has been found acceptable by the Division of Bioequivalence.

3. The dissolution testings conducted by Genpharm Inc. on its sotalol hydrochloride tablets, 80 mg, 160 mg, 240 mg, have been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of 0.1 N HCL at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

   Not less tha f the labeled amount of sotalol in the dosage form is dissolved in 30 minutes.

4. The waiver of bioequivalence requirement for the 80 mg and 160 mg strengths of the test product is granted per 21 CFR 320.22(d)(2).

Lin-Whei Chuang 3/9/98

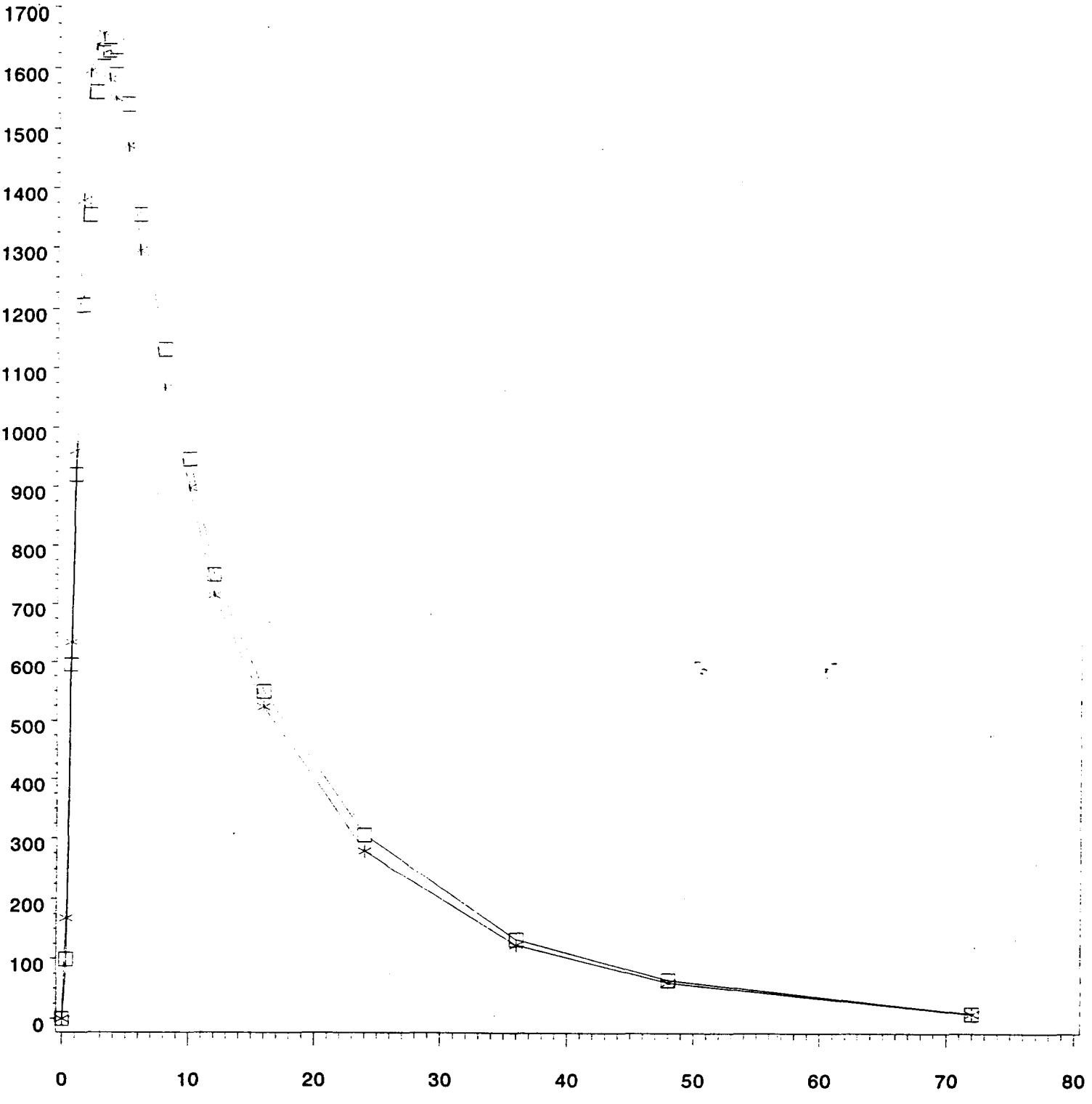
Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG Y.T. Huang 3/9/98

Concur Dale Conner Date: 3/25/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

FIG 1 . PLASMA SOTALOL LEVELS

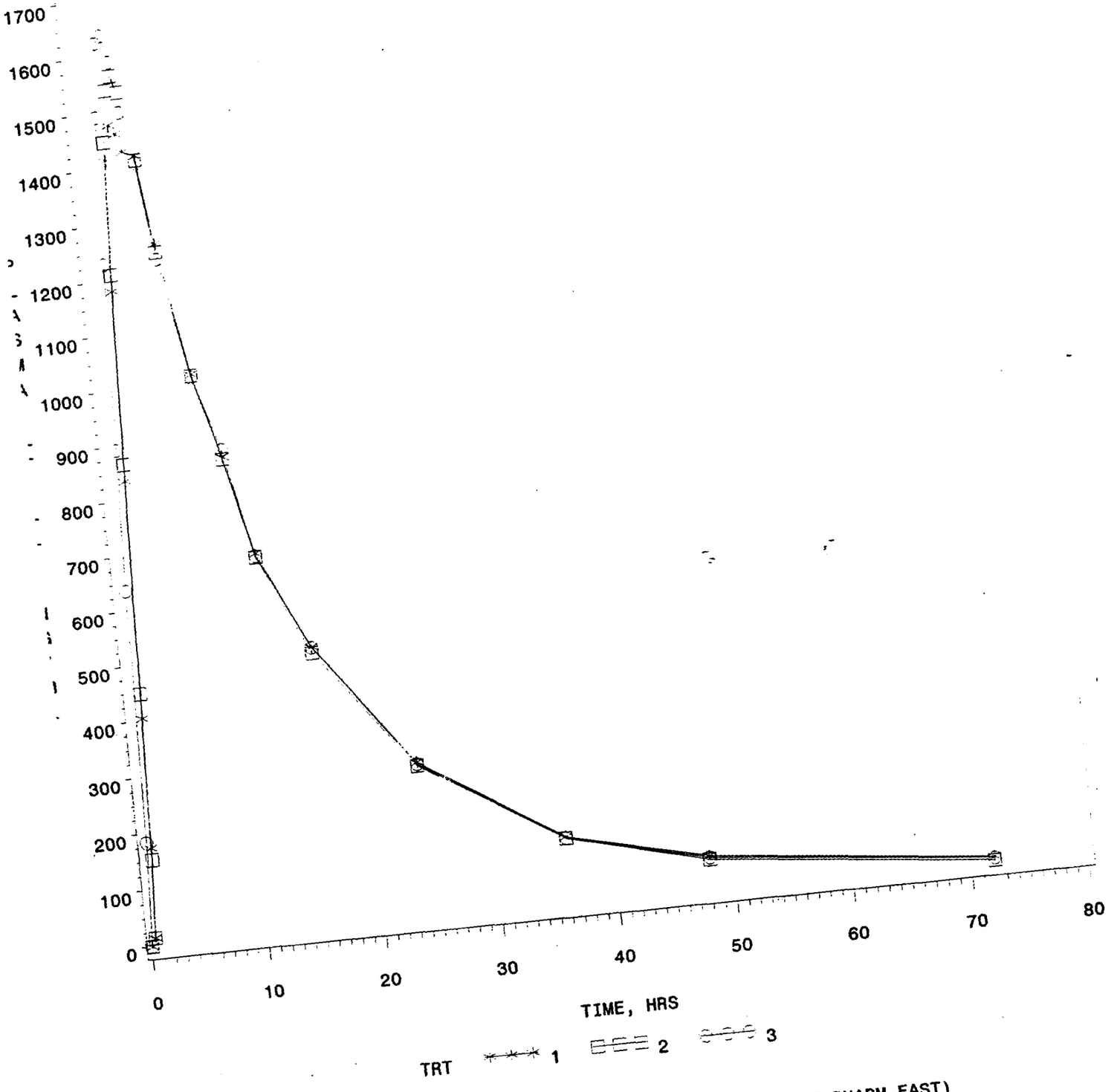
SOTALOL HCL TABLETS, 240 MG, ANDA #75-237
UNDER FASTING CONDITIONS
DOSE=1 X 240 MG



1=TEST(GENPHARM) 2=REF(BERLEX)

FIG 2 PLASMA SOTALOL LEVELS

SOTALOL HCL TABLET, 240 MG, ANDA #75-237
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 240 MG



1=TEST(GENPHARM-FOOD) 2=REF(BERLEX-FOOD) 3=TEST(GENPHARM-FAST)

file ANDA 75-237

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-237 **SPONSOR : Genpharm Inc.**
DRUG & DOSAGE FORM : Sotalol Hydrochloride Tablets
STRENGTHS : 80 mg, 160 mg, 240 mg
TYPES OF STUDIES: One fasting BE study on the 240 mg strength, and one limited food study on the 240 mg strength;
Dissolution testings on all strengths; and
Waiver request for the 80 mg and 160 mg strengths.

CLINICAL STUDY SITE: Biovail Corporation International, Toronto, Canada
ANALYTICAL SITE : Same as clinical study site.

STUDY SUMMARY OF FASTING STUDY ON 1X240 MG TABLET (N = 24):

PARAMETER	TEST LSM	REF.LSM	RATIO T/R	90% CI
AUCI	24097.00	25006.84	0.96	92.32 - 100.41
AUCT	23413.60	24335.50	0.96	92.05 - 100.37
CMAX	1944.43	1842.72	1.06	98.16 - 112.88
LAUCI	*23570.93	*24597.03	**0.96	91.00 - 100.91
LAUCT	*22885.89	*23917.63	**0.96	90.75 - 100.89
LCMAX	*1897.33	*1819.45	**1.04	97.20 - 111.88

* = Geometric LS Mean, ** = Ratio of Geometric LS Means

STUDY SUMMARY OF LIMITED FOOD STUDY ON 1X240 MG TABLET (N = 18)

PARAMETER	LSM TRT. A TEST-FED	LSM TRT. B REF.-FED	LSM TRT. C TEST-FASTING	RATIO OF A/B	RATIO OF A/C
AUCI	22412.98	22099.54	23207.80	1.01	0.97
AUCT	21742.12	21417.12	22608.21	1.02	0.96
CMAX	1674.41	1716.55	1826.62	0.98	0.92
LAUCI	*22155.27	*21847.06	*22920.78	**1.01	**0.97
LAUCT	*21477.79	*21172.06	*22313.33	**1.01	**0.96
LCMAX	*1648.07	*1684.04	*1794.48	**0.98	**0.92

* = Geometric LS Mean, ** = Ratio of Geometric LS Means

The result of both studies are acceptable.

DISSOLUTION :
Conditions: Paddle, 50 RPM, 900 mL of 0.1 N HCl
Q = __ in 30 min.
(Recommended by the Agency, Non-USP Product)

The dissolution data of all three strengths are acceptable.

WAIVER REQUEST:
The formulations of all 3 strengths are proportionally identical. The waiver for the 80 mg and 160 mg strengths is granted per 21 CFR 320.22(d)(2).

PRIMARY REVIEWER :Lin-Whei Chuang BRANCH : I

INITIAL : LWC DATE : 3/9/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : YHuang DATE : 3/9/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE : Dale Conner, Pharm.D.

INITIAL : DPC DATE : 3/25/98